

# The Eighth Day of Creation: looking back across 40 years to the birth of molecular biology and the roots of modern cell biology

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**ABSTRACT** Forty years ago, Horace Judson's *The Eighth Day of Creation* was published, a book vividly recounting the foundations of modern biology, the molecular biology revolution. This book inspired many in my generation. The anniversary provides a chance for a new generation to take a look back, to see how science has and hasn't changed. Many central players in the book, including Sydney Brenner, Seymour Benzer, and François Jacob, would go on to be among the founders of modern cell biology, developmental biology, and neurobiology. These players come alive via their own words, as complex individuals, both heroes and anti-heroes. The technologies and experimental approaches they pioneered, ranging from cell fractionation to immunoprecipitation to structural biology, and the multidisciplinary approaches they took continue to power and inspire our work today. In the process, Judson brings out of the shadows the central roles played by women in many of the era's discoveries. He provides us with a vision of how science and scientists have changed, of how many things about our endeavor never change, and of how some new ideas are perhaps not as new as we would like to think.

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In 1979 Horace Judson completed a 10-year project about cell and molecular biology's foundations, unveiling *The Eighth Day of Creation*, a book I view as one of the most masterful evocations of a scientific revolution (Judson, 1979). I was a college junior, with a vague idea of pursuing marine biology, and course choices restricted by late registration left me in Virology. That course, opening my eyes to the fact that cells are filled with tiny, remarkable machines, set me on a collision course with Judson's book, and together they shaped my path into science. I was not alone. Jeremy Bernstein of the *New York Times* called it "one of the best books of popular or semipopular science writing I have ever read" (Bernstein, 1979), and the Howard Hughes Medical Institute's Sean Carroll rated it one of the five best books about biology (Marchant and Carroll, 2018).

Judson was neither a scientist nor a historian (Grimes, 2011)—instead, he was a self-described "journeyman theatre critic and book reviewer" who sometimes "did science reporting." He was best



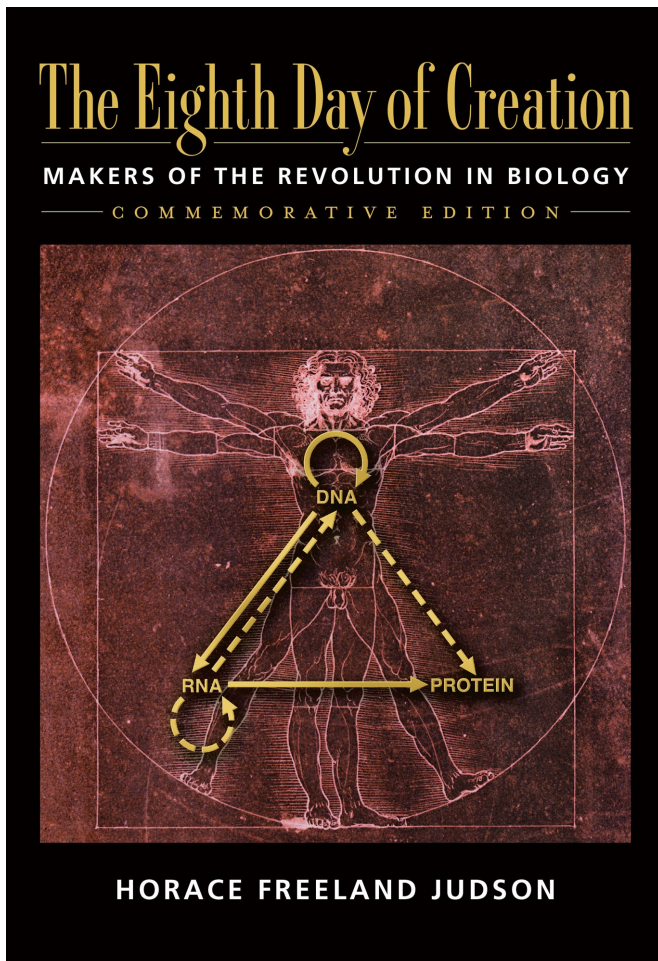
**FIGURE 1:** Horace Judson. Photo printed with permission of the Max Planck Institute for Evolutionary Anthropology.

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**FIGURE 2:** Cover of the commemorative edition of *The Eighth Day of Creation: Makers of the Revolution in Biology*, published by Cold Spring Harbor Laboratory Press.

known for a contentious 1965 interview with Bob Dylan. Judson's book emerged from an almost chance meeting with Max Perutz, a founder of protein crystallography, while writing a piece about "molecular biology" for the *New Yorker*. This began a multiyear friendship that made Judson an honorary member of Cambridge's MRC labs, one birthplace of molecular biology. Subsequent conversations with Jacques Monod and Matt Meselson sharpened his focus, and then the work began.

He ultimately organized the book into three sections, each unique in style as well as content. The first third covers the now well-known race to discover DNA's structure—Judson frames this as a play, whether tragedy or comedy not clear, complete with a list of *dramatis personae*. The middle third follows the unraveling of the central dogma, coding, mRNAs, and the basics of gene regulation. This combines deep dives into the lives of central players, particularly Jacques Monod, François Jacob, and Sydney Brenner, with moment-by-moment narratives of key experiments or scientific meetings. The third section tells the story of Perutz and colleagues' relentless efforts to invent protein crystallography—here the science is covered in depth, complete with illustrations of key principles.

### BRINGING SCIENCE ALIVE

The book's central triumph is how it brings alive in brilliant detail scientists and their science. Judson interviewed 134 scientists and

family members; for many central players, these interviews extended over years. He also obtained access to the correspondence of Sydney Brenner, Francis Crick, Jacques Monod, Lawrence Bragg, and Matt Meselson, from an era when letters were still the primary form of personal and scientific correspondence, and he delved deeply into the literature and, at times, the original notebooks. This makes the storytelling remarkably vivid, providing day-to-day detail, often in the scientists' own words. Judson opened my eyes to the idea that science was done by real people, diverse in personality and approach, and showed me how this shaped their science. This was clear from the book's publication: Bernstein noted "It is as if one were in the classroom with a dozen or so of the world's greatest biologists, with Mr. Judson acting as the informed student." "We learn as he is learning" (Bernstein, 1979).

The material emerging from these interviews, and Judson's meticulous efforts to dig into the scientists' notebooks as well as their memories, make this book special. Judson often adds simple hand-drawn diagrams replicating what scientists drew as they explained their work to him. My favorite was an incredibly vivid description of the progression to the idea of mRNA, with François Jacob at the blackboard.

Key discoveries are laid out moment by moment, in the scientist's own words. For example, Matthaei and Nirenberg's Nobel Prize effort to use synthetic RNAs to decipher the genetic code is framed by Judson and Matthaei going over the relevant notebook together. "And here it says, 'Determine whether phe or tyrosine' You know, this was the final experiment; I had grouped them all; the final group was this two" (p. 477). Another extended thread involves the discovery that inducing a bacterial operon required new gene expression. This included a crazy yet brilliant experiment in which Monica Riley and Art Pardee incorporated radioactive phosphorus into bacterial DNA, froze the bacteria long enough to let radioactive decay destroy the genome, and then reawakened the bacteria to see whether you could induce the operon. Similarly, Judson describes the famous "Good Friday meeting," when the British and French groups compared notes and the idea of mRNA emerged. You feel you are at the party at the Crick's that evening, watching Brenner and Jacob disappear to begin planning the experiment to definitively determine whether new ribosomes were made to induce new protein. Judson then begins an extended page-turner as Jacob and Brenner, visiting Matt Meselson's lab, use precious heavy isotopes (from the Soviet Academy of Science via Linus Pauling, who was a member!) in this effort. Their daily failures, including efforts to hide a now-radioactive piece of equipment, illuminate the final success.

### HEROES AND ANTI-HEROES

By allowing scientists to speak in their own words and by interviewing people across the field, Judson enables his protagonists to come fully alive, not just as scientists but as colleagues, mentors, or competitors. James Watson is revealed as I had come to expect from his recent comments on race and intelligence, which led Cold Spring Harbor Laboratory, which he led, to revoke all titles and honors conferred on him (Durkin, 2019). The story Watson told about the discovery of DNA's structure in his book *The Double Helix* (Watson, 1968) is contrasted with what Judson found in interviews and review of lab notebooks—for example, Judson presents Watson's letter to his mentor Delbruck before the first paper was published. In it, Watson claims "the only X ray consideration [used in the model] was the spacing between the base pairs ... originally found by Astbury" (p. 176), not mentioning using Rosalind Franklin's data. Judson's interviews with Franklin's colleague Aaron Klug and their joint

examination of her notebooks brought to light many new facts (further amplified in Brenda Maddox's biography; Maddox, 2002). While I was unsurprised by Watson's behavior, Wilkins, Franklin's superior, emerges as culpable as well, as he works with Watson and Crick behind Franklin's back, telling them, "I will tell you all I can remember & scribble down from Rosie" (p. 163), and then spends his interviews with Judson trying to justify his actions.

However, set against these lapses are portraits of remarkable scientists—fully human, not without faults, who live remarkable lives within and outside the lab. There is the mountaineer Perutz, escaping the Nazis before the war, interned as an "enemy alien" and then spending the war designing a battleship made of ice (Ferry, 2007). Perutz's decades-long effort to invent protein crystallography, built on a vision of hemoglobin as a living machine, is fascinating. François Jacob left France as the Nazis invaded, returning with the Free French Army, only to be seriously wounded by a shell blast. The story of his subsequent entry into science is told in amusing detail. After being turned down multiple times in efforts to join Lwoff's lab, Jacob returned to ask a final time. In Judson's book Jacob relates "that then [Lwoff] asked 'Would it interest you to work on phage?' I stammered out that was exactly what I had hoped ... Jacob went down the stairs, out to the street, into the first bookstore to find a dictionary (to look up the word phage)" (p. 385). Judson also includes extensive interviews with Sydney Brenner, revealing how a shoemaker's son from South Africa charmed a network of colleagues who helped land him a position at the nascent MRC labs. His wit and insights, which became as much a part of his legend as his discoveries, fill many pages.

Among these, the person who fascinated me, and perhaps Judson, the most was Jacques Monod. Son of a painter and a serious musician himself, his life and personality, with its many facets, could fill a book (and have, see Carroll, 2013). There is the 25-year-old bon vivant who turned down the chance to go on a scientific sea voyage to Greenland to travel to Caltech with Boris Ephrussi. Surrounded by giants in several fields, including Linus Pauling, Thomas Hunt Morgan, Hermann Muller, Edwin Bridges, and Alfred Sturtevant, Monod infuriated Ephrussi by spending the visit organizing and conducting a Bach Society Choir and hanging out with LA socialites. Judson quotes Ephrussi: "Monod has incredibly wide culture; he is very gifted in many fields. But when I knew him first he was a real spoiled child ... I took him to Pasadena. And this was a complete flop ... He really made my life miserable" (p. 357). Finally choosing science over music, there is the Monod of the war years, working in a small lab while rising to lead the Resistance Forces in Paris as a member of the French Communist Party. Judson details this and Monod's break with the Communist Party after the war, interviewing his colleagues both scientific and in the Resistance. Details make the story: "That winter, in an American army mobile library, Monod began catching up with some of the scientific publications that has been unavailable during the Occupation. He came across the issue of *Genetics* that carried Luria and Delbruck's report of the fluctuation test. His own demonstration that bacteria mutate was confirmed and generalized. Soon after that he read Oswald Avery's paper identifying DNA as the transforming principle" (p. 367). The remarkable story of how Monod, Jacob, and colleagues laid the foundation for our understanding of both enzymatic and gene regulation follows, enlivened by their own words and fueled by the close relationships Judson strikes up with them. The episode ending the book exemplifies this: "The afternoon was plucked from time. We talked again about the Lysenko controversy and about the work he had done at the Institut Pasteur during the war. The housekeeper brought a salad of lettuce, the dressing *fines herbes*. She brought a plate of five cheeses. Monod poured a little more wine" (p. 616).

## HIDDEN FIGURES

Rereading the book this year, I was struck by something I missed the first time. While most central players are men (and almost all scientists of the time were white), women made major contributions throughout. These include the handful of women of the time appearing in our textbooks: Rosalind Franklin of DNA fame, and future Nobel laureates Dorothy Hodgkin and Barbara McClintock, the discoverer of transposons who also did fundamental work on gene regulation. Judson brings Franklin alive. Because she died long before the book, he crafts her story through conversations with colleagues, particularly Aaron Klug, who worked with her late in her life, inheriting her correspondence and notebooks. Once again, the story is told through words of her colleagues and competitors. For example, Gosling, her PhD student, notes, "But we used to have terrific arguments together. Her great strength was that you could have this very frank discussion about the work and it never got personal, it was objective and it would push along to reach somewhere" (p. 149).

Even the few who survived the discriminatory system to become group leaders faced major challenges. Dorothy Hodgkin, who solved penicillin's and insulin's structures, and who, as Judson records, gave Max Perutz a key hint needed to solve hemoglobin's structure, is the only woman in the book who led her own group. In the view of the press of her day she was an anomaly. As Athene Donald notes (Donald, 2014), when Hodgkin was awarded the Nobel Prize in 1964, "The Daily Telegraph announced, 'British woman wins Nobel Prize—£18,750 prize to mother of three.' The Daily Mail was even briefer in its headline 'Oxford housewife wins Nobel.' The Observer in its write-up commented 'affable-looking housewife Mrs. Hodgkin' had won the prize 'for a thoroughly unhousewifely skill: the structure of crystals of great chemical interest.'"

Via Judson's book, it becomes clear that women played key roles in British, French, and U.S. labs, as PhD students, postdocs, and technicians. For example, when discussing the Monod and Jacob labs Judson notes, "Of the French in the lab, many were women: Alice Audureau [a PhD student], Madeline Jolit [a technician], Anne-Marie Torriani [a postdoc, later professor at MIT], Germaine Cohen-Bazire [also a postdoc, and later a professor pioneering studying cyanobacteria at the Pasteur]." Discussing the lab where Rosalind Franklin worked, Judson tells us, "Although it's true that women were often discriminated against in science in England then, it's also true that Randall's biophysics lab at King's College London offered better opportunities to women scientists than most places did ... Numbers fluctuated but out of thirty-odd professional scientists there, toward the end of Franklin's second year 8 or 9 were women and 4 of those outranked her" (p. 148). Judson interviewed seven of them.

Throughout the book, Judson documents major discoveries made by women, many of whom went on to become among the first generation of female faculty in cell and molecular biology. Lise Hecht and Mary Stephenson, research associates with Paul Zamecnik, helped discover tRNA and its role in protein synthesis. Esther Lederberg identified the lysogenic strain of *Escherichia coli*, K12, which became the field's standard, and the phage it hosted, lambda, which was key to unraveling gene regulation. Monica Riley worked with Art Pardee to determine that gene expression is necessary for enzyme induction—she went on to the faculty at the University of California, Davis, the State University of New York, and the Marine Biological Laboratory, and was a leader in curating the *E. coli* genome. Rose Litman, also with Pardee, identified 5-bromouracil's mutagenic effect, and Alice Orgel found that mutations caused by it could not be reverted by proflavine, key piece in genetic triplet code proof. Orgel, an MD/PhD who went on to the faculty at the



University of California, San Diego, was referred to by Brenner as “Mrs. Alice Orgel,” reflecting the times. Maxine Singer, a postdoc with Leon Heppel at the National Institutes of Health, pioneered polyribonucleotide synthesis, producing copolymers used by Matthaei and Nirenberg to break the genetic code. She later headed a National Cancer Institute lab studying chromatin and retrotransposons, became president of the Carnegie Institution, and organized the Asilomar Conference to establish guidelines for recombinant DNA research. Hilary Muirhead, a PhD student with Perutz, solved the structure of human hemoglobin and went on to be a professor at Bristol. These are just some of many examples. Some “hidden figures” actually were “computers,” like their astronomical colleagues—Perutz had teams of women measuring spot intensities on x-ray film. Some, like Leslie Barnett, moved into experimental science—she worked with Ingram on sickle cell hemoglobin and with Crick and Brenner to prove the genetic code was triplet. She helped set up Brenner’s lab in Singapore and became a fellow and tutor at Cambridge.

### PLUS ÇA CHANGE...

Rereading Judson this year also reinforced the fact that, while science has advanced tremendously, many features remain unchanged. First is the importance of new technology. Crick notes, “Molecular biology made progress for several reasons. The experimental techniques have been very powerful. Radioactive tracers, electron microscopy, antibodies as tools to dissect the processes” (p. 207). In fact, the last third of the book chronicles development of a new technology—protein crystallography. Judson does this brilliantly, walking you through the physics, once again with hand-drawn diagrams and complete with an appendix. To make this more accessible, he includes a well thought out analogy to the complex harmonics of different musical instruments. Judson also emphasizes the power of interdisciplinary approaches. In his view, “Molecular biology arose in the synthesis of particular lines from five distinct disciplines ... genetics, X-ray crystallography, microbiology, biochemistry, and physical chemistry” (p. 607). He describes how Palade and Porter’s work on electron microscopy empowered the discovery of ribosomes, revealing how scientists pushed the technical envelope, linking electron microscopy, biochemistry, and nascent molecular biology to define how and where proteins are synthesized. This featured the first uses of antibodies in cell biology, as Monod and Melvin Cohn essentially invented immunoprecipitation.

Another theme is science’s international nature and the importance of communication across national and disciplinary boundaries, powerfully illustrated by the frequent and consequential exchanges among Paris, Cambridge, and Cal Tech. In the 1950s, much of this involved exchanges of letters (have my younger readers heard of them?). Judson’s access to the correspondence of key players illuminates the power of letters in exchange of ideas (along with bacterial and phage strains!), interesting in our age of emails and bioRxiv. Extended visits between labs powered science—the list of people passing through Paris is particularly impressive, including one of my scientific “grandfathers,” Dave Hogness, a Monod postdoc in whose lab my graduate advisor Welcome Bender would later begin cloning *Drosophila*’s Hox genes. Judson notes: Lwoff’s group, “marked by its visitors, got the reputation at the Pasteur of being thoroughly Americanized, even to the hours they worked and the fact that no one went out to lunch” (p. 378).

Human nature also never changes, even in small ways. For example, in discussing the scientific meeting in Moscow where the solution to the genetic code was announced, Judson notes: “Meselson had been asked to give a paper on a later day of the

Congress; otherwise he skipped most of the meetings to talk to scientists” (p. 469). Young cell biologists will not be surprised to see Watson write in July 1954 that “The Physiology Course [at Woods Hole] is frightfully intense, and I have never worked so hard in my life” (p. 276).

However, there also are key differences between science then and now. With fewer tools, things moved more slowly, and this had many consequences. Career trajectories were different. In 1947, Benzer, already an assistant professor of physics at Purdue, read Schrödinger’s book and wanted to apply physics to biology. Through Salvador Luria, he took Cold Spring Harbor Laboratory’s phage course. He then went on a remarkably extended leave of absence to master biology, spending 2 years as a postdoc at Cal Tech and a year in Lwoff’s Paris lab. Perhaps most striking are the differences in criteria for publication. Papers were accepted or rejected, but none of the principals talk about the extra year’s experiments needed after review. Even more striking, major journals published speculative ideas. A “Letter” to *Nature* could still be just that—for example, Gamov published one entirely centered on a speculative idea about the genetic code, complete with hand-drawn pictures. His ideas, while ultimately wrong, were critical to moving the field forward and opened up themes still resonating today. “If genes were DNA, ... formed of only four kinds of nucleotides..., ‘It follows that all hereditary properties of any living organism can be characterized by a long number ... written in a four digital system, and containing many thousands of consecutive digits ... the number of the beast ... The numbers describing two different members of the same species must be very similar to one another (though not quite identical, unless they belong to a pair of identical twins) whereas the numbers presenting the members of two different species must show larger differences’” (p. 250).

### A VIEW OF THE FUTURE, IN RETROSPECT

The protagonists also looked forward, envisioning new technical horizons. Judson quotes Crick: “But the question arises, for the new areas that molecular biology is going into, like development and differentiation or neurobiology, are the techniques adequate? It seems highly probable that new techniques are going to be needed” (p. 208). They also imagined the new insights emerging from these technical advances. Prominent among these were the impact of molecular insights on evolutionary biology and medicine. Judson traces this idea back to Reichardt in 1909, whose compendium of hemoglobin crystals was to be used to plot evolutionary relationships among species. Crick, in 1957, noted, “This ‘family likeness’ between the ‘same’ protein molecules from different species is the rule rather than the exception” (p. 335). Citing Sanger’s examination of insulin from five species, he states, “Before long we shall have a subject which might be called ‘protein taxonomy’ ... it can be argued that these sequences are the most delicate expression possible of the phenotype of the organism ... and that vast amounts of evolutionary information may be hidden away within them.” In fact, Pauling, followed by Crick and Ingram, had already laid the foundation of today’s precision medicine, unveiling sickle cell as a molecular disease. Crick noted, “If only [this work] would get started I would put up a case to the MRC for ‘molecular genetics’” (p. 309).

However, some of today’s “new ideas” are not so new. Do you like the current wave of single-cell sequencing and other approaches to explore variability and noise in biological systems? Synchronizing bacteria was impossible in the 1940s and 1950s, so Lwoff cultured a single bacterium in individual wells to observe the time course of lysogeny or phage production. Similarly, Linus Pauling pioneered metabolomics. As I started graduate school, people made light of

his promoting vitamin C, but in fact his “orthomolecular medicine” was seeking to “to analyze people, their metabolisms, accurately enough to determine genetic characteristics that are related to disease” (pp. 91–92). In conversation with Judson, Pauling lays out longitudinal studies of 400 metabolites in urine when people are on a standard diet, attempting to eliminate variation due to the microbiome or, as he put it, “variation due to differences in the bacteria in the gut, because people do have different flora.” Do you think today’s push toward multidisciplinary approaches is new? In 1921, Morgan, considering the discovery of bacterial viruses, said: “Hence we cannot categorically deny that perhaps we may be able to grind genes in a mortar and cook them in a beaker after all. Must we geneticists become bacteriologists, physiological chemists, and physicists simultaneously with being zoologists and botanists? Let us hope so.” Similarly, in 1947, in applying for a graduate fellowship, Crick described his goal as creating “the chemical physics of biology.”

## RETURNING TO THE CELL BIOLOGY OF DEVELOPMENT

As a budding scientist, one thing that captivated me most about Judson’s book was seeing how these scientific leaders envisioned the future. Once again, Judson’s interviews include extended interludes on this. Some are amusing, like Brenner’s thoughts on the future role of computational tools: “‘There will be no difficulty in computers’ being adapted to biology,’ he said with clenched teeth. ‘There will be Luddites. But they will be buried’” (p. 221).

Most influential for me were descriptions of how three molecular biology pioneers—Brenner, Benzer, and Jacob—turned to study the cell biology of development, neuroscience, and behavior. They saw this as a “return,” reversing “Morgan’s deviation.” Brenner again: “Morgan, before 1900, was working on regeneration and embryology ... He gave that up, because, he said, the problems were intractable. He went into the new field of genetics in the hope that it might cast light on the problems of development” (p. 2015). Monod similarly noted: “Morgan was an embryologist. To the extent that we might say he went from embryology to genetics because he felt the genetic problem had to be solved before we could even begin to think about the embryological problem” (p. 271). Morgan’s Nobel in 1933 came just as he was finishing his book *Embryology and Genetics*. In the prize lecture Morgan said: “Between the characters that are used by the geneticist and the genes that his theory postulates lies the whole field of embryonic development, where the properties inherent in the genes become explicit in the protoplasm of the cells” (p. 2017). Brenner notes: “In one way, you could say, all the genetic and molecular biological work of the last sixty years could be considered as a long interlude—sixty years of following out Morgan’s Deviation into the tractable genetic problems. And now ... we have come full circle—back to the problems they left behind unsolved ... How does the egg form the organism?” (p. 209). These discussions seem even more remarkable in retrospect. As the book came out, Christiane Nüsslein-Volhard and Eric Wieschaus were well into their screen for genes shaping the fruit fly body plan, work first published in 1980 (Nüsslein-Volhard and Wieschaus, 1980), and Ed Lewis’s influential paper on how Hox genes shape *Drosophila*’s body plan had just been published (Lewis, 1978)—they would share the 1995 Nobel Prize in Medicine or Physiology.

The conversations in this section are captivating, remarkable, and point 40 years ahead to current challenges in our field. “Sydney Brenner asserted across the high table at King’s College Cambridge: ‘If you say to me, here is a hand, here is an eye, how do you make a hand or an eye, I must say it’s necessary to know the program, to

know it in machine language which is molecular language, to know it so one could tell a computer to generate a set of procedures for growing a hand, or an eye’” (p. 22). [Later, over a glass of port, he continued] “It is an empirical question to find out that description. What is going to be difficult is the immense amount of detail that will have to be subsumed. The most economical language of description is the molecular, genetic description that is already there. We do not know, in that language, what the names are. We cannot say that the organism has a name for a finger ... It is necessary to know the exact number and sequence of the genes, how they interact, what they do. We have to know the program, and know it in machine language, which is molecular language ... We are trying to approach it in two ways. Through the whole organism by doing genetic analysis of mutants and so on—the rather classical approach, which depends on the choice of the animal and how deeply you go into it. But the real way, the way one will have to employ in the long run, is actually to work with cell culture, to build organs. Step by step, we will have to make a retina in cell culture” (p. 219).

## SOME CLOSING ADVICE FOR US ALL

The scientists interviewed also offer advice for those following in their footsteps. Crick relates that “from Bragg and Pauling I learned how to see problems, how not to be confused by the details, and that is a sort of boldness; and how to make oversimple hypotheses—you have to, you see, it’s the only way you can proceed—and how to test them, and how to discard them without getting too enamored of them ... Just as important as having ideas is getting rid of them” (p. 41). Perutz similarly spoke of the power of boldness. “I got the idea ... that you could discover the mechanisms of [enzymes] catalytic function if you could succeed in determining their structure. This idea of Bernal’s was daring, and much more imaginative than anything the enzymologists were thinking of—then or even twenty years later” (p. 507). “It took 23 years before the first protein molecule was solved. But Bernal was one of the most imaginative scientists I have ever met. He could see the possibilities in his first step.” Crick extended this idea: “We have three or four bits of data, we don’t know which one is reliable, so we say, now, if we discard that one and assume it’s wrong—even though we have no evidence that it’s wrong—then we can look at the rest of the data and see what we can make sense of that. And that’s what we do *all of the time*.” In an era of huge data sets, it might be good to think about the implications of this advice.

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